(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 009 686
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 79103432.5

(22) Date of filing: 13.09.79

(51) Int. Cl.³: A 61 K 31/71
C 07 F 9/38

(30) Priority: 14.09.78 US 942364
14.08.79 US 66314

(43) Date of publication of application:
16.04.80 Bulletin 80/8

(84) Designated Contracting States:
BE CH DE FR GB IT NL SE

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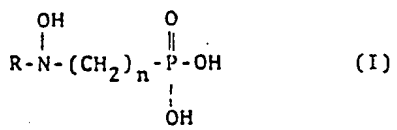
(54) Antibacterial composition comprising a phosphonic acid derivative.

(57) Antibacterial composition comprising a phosphonic acid derivative of the formula:



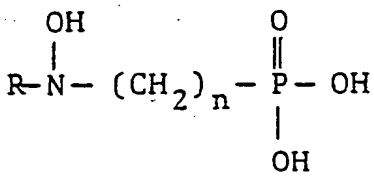
(I)

wherein R is lower alkanoyl and
n is an integer of 2 to 5
or its pharmaceutically acceptable salt and an aminoglycoside antibiotic or its pharmaceutically acceptable salt, and use of said antibacterial composition for the treatment of infectious disease caused by pathogenic bacteria in infected human being or other animals.

EP 0 009 686 A1

Detailed Description:

The present invention relates to a new antibacterial composition and to a new use thereof for the treatment of infectious diseases caused by pathogenic bacteria. More particularly, it relates to an antibacterial composition comprising a phosphonic acid derivative of the formula:



(I)

wherein R is lower alkanoyl and
n is an integer of 2 to 5
or its pharmaceutically acceptable salt and an aminoglycoside antibiotic or its

pharmaceutically acceptable salt, and to a use of said antibacterial composition for the treatment of infectious disease caused by pathogenic bacteria in infected human being or other animals.

The phosphonic acid derivative (I) is an antibiotic having antibacterial activity against various pathogenic bacteria and can be produced by fermentation and/or chemical synthesis, the details of which are described in Belgian Patent No. 857.211.

On the other hand, aminoglycoside antibiotics are well known in a person skilled in the art.

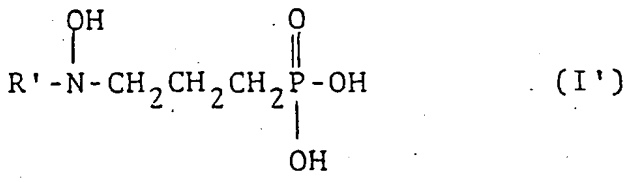
However, such antibiotics can not be said to be entirely sufficient in the treatment of infectious disease, that is, there are pathogenic bacteria against which the phosphonic acid derivative (I) and the aminoglycoside antibiotics alone show no or less antibacterial activity enough to effectively treat human being and other animals for infectious disease or to effectively prevent them from such diseases.

As a result of extensive study of the present inventors, it has been newly found that the phosphonic acid derivative (I) or its pharmaceutically acceptable salt exhibits a synergistic antibacterial activity by combination with an aminoglycoside antibiotic or its pharmaceutically acceptable salt, that is, the combination of the phosphonic acid derivative (I) or its pharmaceutically acceptable salt with the aminoglycoside antibiotic or its pharmaceutically acceptable salt shows an effectively stronger antimicrobial activity against various pathogenic bacteria in human being and other animals, against which the phosphonic acid derivative (I) or the aminoglycoside antibiotic alone shows no or less antibacterial activity enough to effectively treat

human being and other animals for infectious diseases or to effectively prevent them from said diseases.

The antibacterial composition of the present invention comprises a combination of the phosphonic acid derivative (I) or its pharmaceutically acceptable salt and an aminoglycoside antibiotic or its pharmaceutically acceptable salt.

With regard to the phosphonic acid derivative (I) to be used in the present invention, preferred "lower alkanoyl" for R is one having 1 to 6 carbon atoms, among which the most preferred one is formyl and acetyl; and an integer of 3 is most preferred for the symbol "n". That is, the phosphonic acid derivative of the following formula (I') is the most preferred compound to be used in the present invention.



(I')

wherein R' is formyl or acetyl.

Further, the aminoglycoside antibiotic to be used in this invention includes gentamicin, tobramycin, dibekacin, amikacin and bekanamycin, which are famous antibiotics described in e.g. The MERCK INDEX NINTH EDITION pages 565-566, 1220-1221, 395, APP-1 and 693 (1976), respectively.

The pharmaceutically acceptable salts of the phosphonic acid derivative (I) may include a metal salt (e.g. sodium, potassium, calcium, barium or magnesium salt), ammonium salt, an amine salt (e.g. ethanolamine, triethylamine, procaine,

dibenzylamine or dicyclohexylamine salt and the like and that of the aminoglycoside antibiotic may include an acid addition salts (e.g. sulfuric acid salt).

From the above description, it is to be understood that the preferred combination of the phosphonic acid derivative (I) and the aminoglycoside antibiotic is a combination of the phosphonic acid derivative (I') and an aminoglycoside antibiotic selected from gentamicin, tobramycin, dibekacin, amikacin and bekanamycin.

The antibacterial composition of the present invention is useful for treating and preventing infectious diseases induced by pathogenic bacteria in human being and other animals such as poultry, domestic animals, pet animals or experimental animals (e.g. chicken, turkey, duck, quail, cow, cattle, horse, pig, hog, dog, sheep, goat, mink, canary, macaw, mouse, rat or rabbit).

The combination ratio of the phosphonic acid derivative (I) or its pharmaceutically acceptable salt and the aminoglycoside antibiotic or its pharmaceutically acceptable salt in the present antibacterial composition may vary depending on the kinds of pathogens and the symptoms of the patients, to which the present composition is applied, but may usually be selected within a range of 1:1 to 50:1 by weight, preferably 1:1 to 20:1 by weight and most preferably 1:1 to 4:1 by weight.

Further, it is to be noted that the present antibacterial composition may be applied to human being and other animals in conventional forms, examples of which are illustrated as follows.

For applying the present antibacterial composition to human being, it is preferable to apply it in the form of intravenous or intramuscular injection.

It may also be applied locally in the form of a powder, a suppository or an ointment. When used as an injection, it may be applied in admixture with a solid or liquid carrier or diluent which is usually used for the conventional antibiotic injections, and further, may also be applied together with other medicines such as analgesics (e.g. lidocaine) which are usually used in injections. The most preferred carrier or diluent is water. When used as a suppository and an ointment, it may be used in admixture with conventional suppository and ointment bases, respectively.

For applying the present antibacterial composition to other animals, it is preferable to apply it in the form of injection or in the form of infusion. It may also be applied locally in a form of a powder or an ointment. When used as an injection or infusion, it may be applied in admixture with a solid or liquid carrier or diluent which is usually used for the conventional antibiotic injections or infusions. The most preferred carrier or diluent is water, vegitable oils, paraffins or the like. When used as an ointment, it may be applied in admixture with conventional ointment bases.

The dosage of the present antibacterial composition may vary depending on the kinds of the phosphonic acid derivative (I) and the aminoglycoside antibiotic, the combination ratio thereof and various factors such as the weight and age of the patient, the kind and severity of the infection, and the kind of the application mode. However, it is to be understood that, as the dosage of the effective ingredient included in the present antibacterial composition, it may be effectively administered to the patient in a dose of about 0.3 to 20 mg/kg/day.

The total daily amount mentioned above may be divisionally given to the patient at the interval of 6-12 hours per day.

And further, it is to be noted that the present antibacterial composition shows low toxicity as shown in the following toxicity test.

Acute toxicity test:

The acute toxicity test was conducted by using each of the following antibacterial composition according to the following experimental procedure.

(1) Antibacterial composition:

(a) Composition of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (4:1 by weight).

(b) Composition of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and tobramycin (4:1 by weight).

(c) Composition of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and dibekacin sulfate (4:1 by weight).

(d) Composition of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and amikacin sulfate (4:1 by weight).

(e) Composition of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and bekanamycin sulfate (4:1 by weight).

(2) Experimental procedure:

A phosphate buffered saline (pH 6.8) (0.5 ml) containing one of the above antibacterial compositions was intraperitoneally injected into each of three DDY-strain male mice aged at 5 weeks (Dose:50 mg/kg),

respectively. The observation was continued for one week after the administration.

(3) Test results:

All of the test mice were living and normal.

The antibacterial activities and the preventing effectiveness against various bacterial infections of the present antibacterial composition are illustrated in the following experimental tests in vitro and in vivo.

Test 1

Synergistic activity of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin in vitro:

Onto a Nutrient agar (Difco) containing prescribed amount of each of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid, gentamicin sulfate and a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (1:1 by weight), there was spot-inoculated, using a multiple inoculator, cultured broth of each pathogen which was cultured overnight in Nutrient broth (Difco), in a concentration of 10^8 cells/ml. After the incubation was carried out at 37°C for 20 hours. Minimum Inhibitory Concentration (MIC) values were determined.

Further, in order to observe the degree of synergistic antimicrobial activity, Fractional Inhibitory Concentration (FIC) values and FIC Index were calculated from the determined MIC values

according to the following calculation method, respectively.

Calculation method

(a) MIC value of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid: Ao

(b) MIC value of gentamicin sulfate: Bo

(c) MIC value of a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate: Cab

In the case that the combination ratio of a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate is m : n (by weight), each of FIC values and FIC indexes was calculated according to the following equations.

$$\text{FIC of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid} = \frac{\frac{m}{m+n} \cdot Cab}{Ao}$$

$$\text{FIC of gentamicin sulfate} = \frac{\frac{n}{m+n} \cdot Cab}{Bo}$$

$$\text{FIC index} = \frac{\frac{m}{m+n} \cdot Cab}{Ao} + \frac{\frac{n}{m+n} \cdot Cab}{Bo}$$

The test results are shown in the following table 1.

Table 1. Synergism between 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin against pathogenic bacteria

Microorganism	MIC (mcg/ml)			FIC index
	A	B	C	
Pseudomonas aeruginosa No.5	800	50	25	0.27
Pseudomonas aeruginosa No.11	>800	3.13	1.56	< 0.25
Pseudomonas aeruginosa No.12	800	12.5	3.13	0.13
Pseudomonas aeruginosa No.13	800	100	50	0.28
Pseudomonas aeruginosa No.18	>800	50	25	< 0.27

Note) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid

B: Gentamicin sulfate

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (1 : 1 by weight)

Test 2

Synergistic activity of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin in vitro:

Onto a Nutrient agar(Difco)containing prescribed amount of each of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid, gentamicin sulfate and a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (1:1 and 4:1 by weight), there was spot-inoculated, using a multiple inoculator, 10^2-fold dilution of cultured broth of each pathogen which was cultured overnight in Nutrient broth (Eiken), in a concentration of 10^8 cells/ml. After the incubation was carried out at 37°C for 18 hours, MIC values were determined.

FIC values and FIC Index were calculated in substantially the same manner as described in Test 1.

The test results are shown in the following table 2.

Table 2. Synergism between 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid and gentamicin against pathogenic bacteria

Microorganism	MIC (mcg/ml)				FIC index	
	A	B	C	D	C	D
Escherichia coli 99	25	12.5	12.5	15.6	0.75	0.75
Citrobacter freundii 35	100	3.13	3.13	7.81	0.52	0.56
Enterobacter aerogenes 7	100	6.25	6.25	15.6	0.53	0.62
Serratia marcescens 9	200	50	50	62.5	0.62	0.50
Proteus vulgaris 5	25	6.25	6.25	7.81	0.62	0.50
Staphyloccocus aureus 3	400	0.39	0.39	0.98	0.50	0.50

Note to Table 2) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid

B: Gentamicin sulfate

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propyl-phosphonic acid and gentamicin sulfate (1:1 by weight)

D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and gentamicin sulfate (4:1 by weight)

Test 3

Synergistic activity of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and tobramycin; that of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and dibekacin; that of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and amikacin; and that of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and bekanamycin were tested in vitro in substantially the same manner as described in the Test 2.

The test results are shown in the following Table 3, 4, 5 and 6, respectively.

Table 3 . Synergism between 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid and tobramycin

Microorganism	MIC (mcg/ml)				FIC index	
	A	B	C	D	C	D
Citrobacter freundii 35	100	3.13	3.13	7.81	0.52	0.56
Enterobacter aerogenes 7	100	6.25	6.25	15.6	0.53	0.62
Staphylococcus aureus 3	400	0.39	0.39	0.98	0.50	0.50

Note) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid

B: Tobramycin

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and tobramycin (1:1 by weight)

D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and tobramycin (4:1 by weight)

Table 4 . Synergism between 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid and dibekacin

Microorganism	MIC (mcg/ml)				FIC index	
	A	B	C	D	C	D
Escherichia coli 82	100	6.25	6.25	15.6	0.53	0.62
Citrobacter freundii 35	100	6.25	6.25	15.6	0.53	0.62
Enterobacter aerogenes 25	100	6.25	6.25	15.6	0.53	0.62
Proteus mirabilis 48	25	12.5	12.5	15.6	0.75	0.75
Proteus vulgaris 7	25	50	25	15.6	0.75	0.56
Pseudomonas aeruginosa 77	6.25	3.13	3.13	3.91	0.75	0.75
Staphylococcus aureus 2	200	1.56	1.56	3.91	0.50	0.52

Note to Table 4) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid

B: Dibekacin sulfate

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and dibekacin sulfate (1:1 by weight)

D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and dibekacin sulfate (4:1 by weight)

Table 5 . Synergism between 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid and amikacin

Microorganism	MIC (mcg/ml)				FIC index	
	A	B	C	D	C	D
Enterobacter aerogenes 7	100	6.25	6.25	15.6	0.53	0.62
Serratia marcescens 27	400	12.5	12.5	31.3	0.52	0.56
Proteus mirabilis 5	25	3.13	3.13	7.81	0.56	0.75
Pseudomonas aeruginosa 42	50	6.25	6.25	15.6	0.56	0.75
Staphylococcus aureus 1	400	0.78	0.78	1.95	0.50	0.50

Note to Table 5) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid

B: Amikacin sulfate

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and amikacin sulfate (1:1 by weight)

D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and amikacin sulfate (4:1 by weight)

Table 6 . Synergism between 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid and bekanamycin

Microorganism	MIC (mcg/ml)				FIC index	
	A	B	C	D	C	D
Escherichia coli 116	200	200	100	125	0.50	0.63
Enterobacter aerogenes 7	100	6.25	6.25	15.6	0.53	0.63
Enterobacter cloacae 18	200	6.25	6.25	15.6	0.52	0.56
Pseudomonas aeruginosa 42	50	100	25	31.1	0.38	0.56

Note to Table 6) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid

B: bekanamycin sulfate

C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and bekanamycin sulfate (1:1 by weight)

D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and bekanamycin sulfate (4:1 by weight)

Test 4

Synergistic activity of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin in various combination ratios:

Into a Nutrient broth (Difco) containing prescribed amounts of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate, was inoculated 0.5% of 10-fold dilution of cultured broth of pathogen which was cultured overnight in Nutrient broth (Eiken). After the incubation was carried out at 37°C for 18 hours, the growth of the test organism was observed. The results are shown in the following Table 7. In the table, the symbol "+" means that the test microorganism grew and the symbol "-" means that the test microorganism did not grow.

Table 7. Isobologram showing synergy of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin against Klebsiella pneumoniae 8

Monosodium salt of 3-(N-formyl-N-hydroxyaminopropylphosphonic acid (mcg/ml)

Gentamicin sulfate (mcg/ml)	0	0.78	1.56	3.13	6.25	12.5	25
0	+	+	+	+	+	+	-
0.001	+	+	+	+	+	+	-
0.003	+	+	+	+	-	-	-
0.006	+	+	+	+	-	-	-
0.01	+	+	-	-	-	-	-
0.025	+	-	-	-	-	-	-
0.05	-	-	-	-	-	-	-

As seen clearly from the above results in Tests 1 - 4, the combination of the phosphonic acid derivative (I) and the aminoglycoside antibiotic shows synergistic antibacterial activity against various pathogens.

Test 5

Effects on the experimentally infected mice:

ICR-strain male mice weighing 23-25 g (8 mice per one group) were used. Pathogenic bacteria, Pseudomonas aeruginasa 42 suspended in 5% aqueous mucin suspension (10^7 cells/ml)(0.5 ml) was inoculated intraperitoneally into each mouse. One hour after the inoculation, the antibiotics as mentioned in the following table were administered subcutaneously, and then survival of the test mice was measured 4 - 5 days after the infection to determine ED_{50} value. The results are shown in the following Table 8.

Incidentally, FIC values and FIC index in this in vivo test were also calculated from the determined ED_{50} values according to the following calculation method.

Calculation method

(a) ED_{50} value of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid: A'o

(b) ED_{50} value of gentamicin sulfate: B'o

(c) ED_{50} value of a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate: C'ab

In case that the combination ratio of a mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)-propylphosphonic acid and gentamicin sulfate is m:n (by weight), each of FIC values and FIC index was calculated according to the following equations.

FIC of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid

$$= \frac{\frac{m}{m+n} \cdot C'ab}{A'o}$$

$$\text{FIC of gentamicin sulfate} = \frac{\frac{n}{m+n} \cdot C'ab}{B'o}$$

$$\text{FIC index} = \frac{\frac{m}{m+n} \cdot C'ab}{A'o} + \frac{\frac{n}{m+n} \cdot C'ab}{B'o}$$

Table 8. Synergism between 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin in protecting activity

ED_{50} (mg/kg)				FIC index	
A	B	C	D	C	D
>1600	1.99	101.03	40.86	<0.58	<0.81

Note) A: Monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid alone.
B: Gentamicin sulfate alone.
C: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (100:1.03 by weight).
D: A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin sulfate (39.3:1.56 by weight).

As seen clearly from the above results, the synergistic antibacterial activity of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and gentamicin was also confirmed by in vivo test.

The antibacterial compositions of the present invention are illustrated by the following Examples.

Example 1

A sterile mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (80 mg.) and gentamicin sulfate (20 mg.) was put in a sterile vial and the vial was sealed. And when used, the above mixture was dissolved in a sterile water (2 ml.) to give an injection preparation.

In substantially the same manner as described in the above Example 1, there was prepared an injection preparation of an antimicrobial composition as illustrated in the following Examples 2 - 5.

Example 2

A mixture of monoammonium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (120 mg.) and tobramycin (30 mg.) was used as the active ingredient for injection.

Example 3

A mixture of monopotassium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (200 mg.) and dibekacin sulfate (50 mg.) was used as the active ingredient for injection.

Example 4

A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (200 mg.) and amikacin sulfate (100 mg.) was used as the active

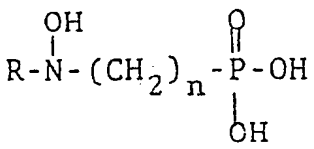
ingredient for injection.

Example 5

A mixture of monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (400 mg.) and bekanamycin sulfate (100 mg.) was used as the active ingredient for injection.

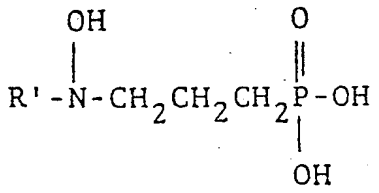
What is claimed is:

1. An antibacterial composition comprising a phosphonic acid derivative of the formula:



wherein R is lower alkanoyl, and
n is an integer of 2 to 5,
or its pharmaceutically acceptable salt and an aminoglycoside antibiotic or its pharmaceutically acceptable salt.

2. The antibacterial composition according to claim 1, wherein the phosphonic acid derivative is a compound of the formula:



wherein R' is formyl or acetyl, and
the aminoglycoside antibiotic is an antibiotic selected from gentamicin, tobramycin, dibekacin, amikacin and bekanamycin.

3. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative or its pharmaceutically acceptable salt and the aminoglycoside antibiotic or its pharmaceutically acceptable salt are contained in a ratio of 1:1 to 50:1 by weight.

4. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative is 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and the aminoglycoside antibiotic is gentamicin.

5. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative is 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and the aminoglycoside antibiotic is tobramycin.

6. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative is 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and the aminoglycoside antibiotic is dibekacin.

7. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative is 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and the aminoglycoside antibiotic is amikacin.

8. The antibacterial composition according to claim 2, wherein the phosphonic acid derivative is 3-(N-formyl-N-hydroxyamino)propylphosphonic acid and the aminoglycoside antibiotic is bekanamycin.

European Patent Office

EUROPEAN SEARCH REPORT

0009686
Application number
EP 79 10 3432

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	DE - A - 2 733 658 (FUSIJAWA PHARMACEUTICAL CO., LTD.) * Claims 1,26-29 *	1
D	& BE - A - 857 211	
	--	
P,A	EP - A - 0 003 618 (FUSIJAWA PHARMACEUTICAL CO., LTD.) * Claims 1-3 *	1

CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)

A 61 K 31/71
C 07 F 9/38

TECHNICAL FIELDS SEARCHED (Int.Cl. ³)

A 61 K 31/71
C 07 F 9/38

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	07-12-1979	BRINKMANN

EPO Form 1503.1 06.78